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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on May 24, 1991 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152 |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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EXAMINER'S ACTION

Claims 1-17 and new claim 18 remain.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

5 Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 18, it is not clear which non-identical sequences are encompassed by the phrase "substantially similar to".

10 The specification is objected to, claims 1-17 remain and new claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention for the reasons set forth on pages 2-3 of the previous office action. Applicants' arguments have been considered but are not deemed persuasive.

15 As recited previously, Applicants have not demonstrated that the synthetic gene exemplified or any other synthetic gene has insecticidal activity. The data set forth in Table 1 indicates that some constructs with modified sequences based upon codon usage do not work much better than the control. Applicants recite that "the synthetic sequences exhibited a much
20 more uniform and greater toxicity to hornworms" (present specification, page 19, lines 18-19). However, it is not clear how this conclusion was reached. The data of Table I indicates high variability, but also that the control was in the same range as plants transformed with synthetic gene constructs (25%-83% for synthetic constructs versus 39% for control). In
25 other words, pTVAMVBT3 and pTVAMVBT4 had kill rates of 46% and 25%, respectively, which appears to be similar to the 39% level for the control. pTVAMVBT2 was significantly higher at 83%. If this construct works consistently better, Applicants may wish to consider limiting their claims to

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this construct. However, with this degree of variability, Applicants' disclosure is not enabling for the broader claims recited and is an "invitation to experiment" in regard to applying the guidelines provided by Applicants to variations falling within the scope of the present claims.

5 Although, the distribution of clones into the "9" rating is slightly higher for the synthetic constructs, it is not clear what criteria were used to establish the various categories 6-9. Furthermore, since the majority of the control plants fell into the "8" category, the relevant question, which does not appear to be addressed in the specification, is whether or not the difference
10 between an "8" and a "9" rating is significant. Moreover, even if these deficiencies were remedied, the specification would only be considered enabling for claims limited as set forth below.

 Applicants admit that the "data of Table I does [s]how some variability" but argue that such variability is an inherent feature of genetic
15 engineering (Amendment B, page 5, first full paragraph). In the face of such admitted variability, it is maintained that Applicants' claims are not enabled as recited. Applicants' claim 1, for example, is not limited to any given procaryotic sequence or any given dicot plant. Furthermore, as pointed out previously, 2 of the 3 constructs exemplified had kill rates similar to the
20 control (see above and previous office action). Thus, it is concluded that this variability constitutes unpredictability such that one skilled in the art would not be able to achieve the invention as now claimed by following the teachings of the specification without undue experimentation.

 Applicants argue that the synthetic sequences achieved a higher
25 rating than the native sequences in Applicants' rating system (Amendment B, pages 5-6, bridging paragraph). However, it was pointed out previously that the differences between the synthetic sequences and the native sequence do not appear significant since generally the native sequence achieved an "8" while the synthetic sequences achieved a "9" rating in this
30 seemingly qualitative and possibly subjective assay and the difference

between a "9" rating and an "8" rating has not been set forth by Applicants. With regard to this last point, Applicants argue that the application clarifies how the categories were established on pages 16-18 (Amendment B, page 6, first full paragraph). However, the only clarification I can find is at present
5 specification, pages 18-19, bridging paragraph where it is stated that "[a] rating of "9" was indicative of a strongly resistant plant, where the high level of toxin present caused rapid cessation of feeding and early death. A rating of "5" or less indicated moderate toxicity, in which generally one or more days of limited feeding occurred before larval death." This still does not
10 indicate to me how long a "9" fed before dying or how long an "8" fed before dying.

The rejection of claims 15-17 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Manduca sexta is withdrawn in view of Applicants' amendments.

15 Claims 1-14 remain rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Manduca sexta and other insect species which can be reasonably extrapolated from the teachings of the examples in the specification. See MPEP 706.03(n) and 706.03(z).

20 As recited previously, a given B.t. toxin does not show toxicity against all insect species (See Hofte et al, Table 5; Vaeck et al, page 37, column 1, for example). Thus, enablement for Applicants' claims appears to be limited to the insect species tested.

25 Applicants argue that "multiple examples are not required [i]f the methodology is made clear and is fully enabling for other examples" (Amendment B, pages 7-8, bridging paragraph). However, in this case, the methodology is not fully enabling for other examples. It was known that native B.t. which was toxic to M. sexta was difficult to express in plant cells and it had been suggested that "translational efficiency might be important" (see Vaeck et al, page 36, column 2, paragraph 2). Thus, it was reasonably

expected that increases in translational efficiency would lead to better expression. However, in the case of other procaryotic genes as broadly claimed, there is no predictability in the result of modification of the sequence for codons used in plant cells. Thus, to practice the invention as
5 broadly claimed would require undue experimentation by one skilled in the art.

The rejection of claims 1-17 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to tobacco is withdrawn in view of Applicants' arguments.

10 The rejection of claims 1-17 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to dicot cells is withdrawn in view of Applicants' amendments.

Claims 1-17 remain rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to claims which recite the
15 upper sequence shown in Figure 2. See MPEP 706.03(n) and 706.03(z).

As recited previously, Applicants have shown only one B. thuringiensis derived synthetic gene which sequence is shown in Figure 2. In view of the unpredictability of expression of foreign genes, it does not appear that any synthetic gene which was functionally equivalent to any Bt
20 toxin protein would be effective in any plant cell against any species of insect or that the method is broadly applicable to any foreign gene expressed in a plant cell as broadly claimed. As Applicants point out themselves, the pattern of codon usage is only one of the mechanisms to which poor expression may be ascribed (Amendment A, page 5, paragraph 2).

25 Applicants argue that the method described is "logically applicable to any of a number of proteins sought to be expressed into plant species" even though "[f]or some genes sought to be expressed in plants, the present method may in fact be very unimportant" (Amendment B, page 10).

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broad
applicability

Applicants' arguments pose the very basis for this rejection. Since there are no guidelines in the specification such that one skilled in the art would know which proteins would benefit from application of the technique, the claims as recited represent an "invitation to experiment". Thus, undue
5 experimentation would be required by one skilled in the art to practice the invention as broadly claimed.

The rejection of claims 1-17 under 35 U.S.C. 103 as being unpatentable over Hoekema et al taken with Murray et al, Schnepf et al, Vaeck et al, Hollenberg et al, and Seeburg et al is withdrawn in view of the 131
10 Declarations of Michael J. Miller (paper No. 6) and Kenneth A. Barton (paper No. 10).

Claims 1-17 remain and new claim 18 is rejected under 35 U.S.C. 103 as being unpatentable over Hoekema et al taken with Grantham et al, Schnepf et al, Vaeck et al, Barton et al, Hollenberg et al, and Seeburg et al as
15 applied in the previous office action. Applicants arguments have been carefully considered but are not deemed persuasive.

As recited previously, Hoekema et al teach a method of affecting gene expression by exploiting codon usage. Hoekema et al disclose that when foreign proteins are used in yeast vector systems the expression level may
20 decrease one or two orders of magnitude. Hoekema et al teach that the codon choice pattern was one parameter affecting this low level of expression and that expression of native highly expressed yeast genes can be altered by substituting the codons usually found in yeast genes with minor codons which never or rarely occur in highly expressed natural genes. The
25 amino acid sequence was not disturbed. As a result, both mRNA and protein synthesis were decreased.

Hoekema et al differ from the claimed invention primarily in that their work was directed to yeast cells, not plant cells as in the claimed invention. However, modification of a procaryotic sequence to optimize

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expression in a plant cell was well within the ordinary level of skill in the art as shown by Grantham et al (see especially, Tables 1 and 2). More specifically, in Bacillus thuringiensis as reported by Schnepf et al, it was known that the use of A or T was preferred. It was also known that B. thuringiensis toxins in particular were poorly expressed in plant cells as reported for example by Vaeck et al and Barton et al. Furthermore, Barton et al teach the expression of insect toxins in tobacco using the pAMVBTS vector. Thus, it would have been obvious to one of ordinary skill in the art that the concept taught by Hoekema et al in yeast could be applied to expression of foreign genes in plants by modification of known vectors for expression of Bt toxins such as those taught by Barton et al and Vaeck et al in accordance with the guidelines provided by Hoekema et al and Grantham et al.

Methods of transfer of foreign genes to plant cells and expression in plant cells were all well within the ordinary level of skill in the art. Methods of making long oligonucleotides were known in the art as taught by Hoekema et al, Hollenberg et al (Figure 9), and Seeburg et al (Figure 2).

Applicants assert that the "combination of references cited by the Examiner does not indicate with the required degree of certainty that the present strategy would be effective" (Amendment B, page 13, first full paragraph). However, it is noted that none of Applicants' claims are limited to an invention that can be achieved with any degree of certainty. As indicated above and in previous office actions, the only aspect of the invention that appears to be reproducible with a reasonable expectation of success would involve claims which recited the pTAMVBT2 and pTVAMVBT3 plasmids. Although it may be true that the combination of references cited would not lead one skilled in the art to the invention claimed with "certainty", it is maintained that neither would Applicants' disclosure since the disclosure is limited to some success with 2 out of 3 plasmids modifying B.t. sequences and the claims 1-14 broadly recite any

foreign procaryotic protein. Even claims 15-18 include modifications of B.t. sequences which are not enabled by the present specification. Thus, it is deemed that the previously recited rejection is applicable, at least to the extent that the claims are enabled.

5 Applicants argue that it was not apparent from the disclosure of
Hoekema et al whether a modified gene would express well in plants which
included less popular codons since in the gene of Hoekema et al every codon
was a preferred codon (Amendment B, page 13-14, bridging paragraph).
First, Applicants have not limited their claims to the use or avoidance of any
10 particular codons. Second, it is not apparent from the specification that there
are any hard and fast rules developed such as that it was necessary for plant
genes to have codons of less popularity since 1 of the 3 modified plasmids
(pTVAMVBT4) did not work as well as the control.

15 Applicants argue that none of the cited references shows the use of
synthetic gene sequences used in plants (Amendment B, page 14, first full
paragraph). While the primary reference relates to yeast rather than plants,
Hoekema et al do teach the use of synthetic sequences. The use of
oligonucleotides in molecular biology, including plant molecular biology, for a
variety of purposes was well known and Hollenberg et al and Seeburg et al
20 were cited to show methods of making long oligonucleotides.

Applicants argue that it was not predictable that improved expression
could be achieved by modification of less than one third of the total gene
sequence or that the best results would be achieved with the least
modification (Amendment B, pages 14-15, bridging paragraph). However, as
25 pointed out above, none of Applicants' claims are limited to specific
modifications, i.e., specific plasmids which worked. Applicants' results would
indicate that it is not predictable what combination of modifications will
result in effective expression. Applicants argue that "[the cited] references
might be considered an invitation to experiment" (Amendment B, pages 15-

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16, bridging paragraph). However, it is maintained that the cited references teach the claimed invention to the extent enabled by Applicants.

Thus, the rejection set forth previously clearly sets forth a prima facie case of obviousness which has not been overcome by Applicants' arguments.

- 5 The rejection is therefore maintained as the method of improving expression and dicot plants with improved expression are obvious over the prior art, absent evidence to the contrary.

- The European applications 359472 and 385962 have been considered, but these disclosures are not considered to be prior art as the publications
10 dates are after Applicants' filing dates.

No claim is allowed.

- THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month
15 upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

- A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE
20 EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE
25 PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

An inquiry concerning this communication should be directed to Che Swyden Chereskin, Ph.D., at telephone number (703) 308-0034. Inquiries of a general nature should be directed to the Group 180 secretary at (703) 308-0196.

- 5 Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

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CSC
7/17/91

Elizabeth C. Weimar

ELIZABETH C. WEIMAR
SUPERVISORY PATENT EXAMINER
ART UNIT 184

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